DOPAMINERGIC AND NON-DOPAMINERGIC MECHANISMS OF NON-MOTOR SYMPTOMS OF PARKINSON DISEASE

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ABSTRACT

During the last years, the non-motor aspects of Parkinson's disease were in the focus of the attention in Movement Disorders Society and experts. Some clinical and research instruments like NMSS (Non-Motor Symptoms Scale) help clinicians to recognize and evaluate these aspects that are common and occur across all stages of PD. Some non-motor symptoms like sleep problems, autonomic dysfunction and pain are partly dopaminergic but others are non-dopaminergic. When they are treatable, the treatment can increase the quality of life for these patients.

Key words: non-motor, Parkinson's disease, dopaminergic treatment, depression, cognition, sleep disorders, dysautonomia

INTRODUCTION

Non-motor symptoms (NMS) of Parkinson's disease (PD) are common but are often unrecognized in clinical practice because the absence of systematic questioning by health care professionals and also underreport by the patients (1).

They are present in a large proportion of patients with PD (2) and consist of a large variety of symptoms (neuropsychiatric, sensory, sleep disorders, autonomic dysfunction, gastrointestinal and others) (Table 1). Some non-motor symptoms are drug induced and others are related to fluctuations (Table 2).

TABLE 1. *Non-motor symptoms in Parkinson disease*

1. Neuropsychiatric:
– Anxiety
– Apathy
– Depression
– Hallucinations, illusions
– Cognitive impairment (MCI, dementia)
2. Sensory:
– Olfactory disturbance (hyposmia, functional anosmia)
– Pain
– Visual disturbance (blurred vision, diplopia, etc.)
3. Autonomic dysfunction:
– Bladder dysfunction (urgency, frequency, nocturia)
– Sexual dysfunction
– Sweating abnormalities (hyperhidrosis)
– Orthostatic hypotension
4. Gastrointestinal symptoms:
– Drooling of saliva
– Dysphagia
– Constipation
– Nausea
– Vomiting
5. Sleep disorders:
– REM sleep behaviour disorder
– Excessive daytime somnolence, narcolepsy like attacks
– Restless legs syndrome, other periodic leg movements syndromes
– Insomnia
– Sleep breathing disorders
– Non-REM parasomnias (confusional wandering)
6. Fatigue:
– Central
– Peripheral

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TABLE 2. *Non-motor symptoms induced by medication*

1. Dopaminergic drug-induced NMS: – Hallucinations, psychosis – Dopamine dysregulation syndrome – Impulse control disorders
2. Other drug induced NMS: – Ankle swelling – Dyspnea – Skin reactions – Sexual
3. Non-motor fluctuations: – Dysautonomia – Cognitive/psychiatric – Sensory/pain – Visual blurring

Non-motor symptoms occur throughout the course of the disease. Some of them, like depression, fatigue, sexual and olfactory disorders may appear during the earliest stages of the disease in non-treated patients with Parkinson's disease. Sometimes they precede the motor manifestations of the disease with several years. The premotor symptoms include: constipation, olfactory dysfunction (discrimination), REM sleep behaviour disorder (RBD) and depression (3). The occurrence of earlier non-motor symptoms prior to the onset of motor clinical dysfunction would appear consistent with the ascending hypothesis of PD pathology proposed by Braak and colleagues (except the cognitive impairment in the early stages of the disease).

EPIDEMIOLOGY

In the report of Galagher et. al, patients with PD reported an average of 11 non-motor symptoms, but only 5 non-motor symptoms in average are recorded in their medical charts (4). Some questions have been raised about whether non-motor symptoms of PD differ from normal aging. One case-control study answer this question, showing that the frequency of non-motor symptoms were significantly higher among patients with PD in all domains (5).

The frequency of NMS increases along with the disease duration (6). At the time of diagnosis, the prevalence of NMS among patients with Parkinson's disease is 21% (pain, urinary symptoms, depression and anxiety) and goes up to 88% after 7 years of disease progression (6).

Till 2006 there were no available tools for diagnosis of non-motor symptoms (NMS). Using the self-completed non-motor questionnaire (NMS-Quest), the international study of Chaudhuri et al, reported that NMS are highly prevalent in PD patients and confirmed the presence of NMS across all disease stages, the number of symptoms correlating with disease duration and severity (7).

PATHOPHYSIOLOGY OF NON-MOTOR SYMPTOMS

Most of the non-motor features associated with PD are presumably related to the involvement of the non-dopaminergic systems, with the hypothesis of involvement of other neurotransmitters including serotoninergic, noradrenergic and cholinergic transmission (8). Some non-motor symptoms (like depression, anxiety and apathy) are partly related to decreased dopaminergic transmission. The axons from the key dopaminergic areas of the brain (substantia nigra pars compacta, ventral tegmental area and hypothalamus) form four pathways (mesocortical, mesolimbic, nigrostriatal and tuberoinfundibular). These pathways seem to be implyed in the appearance of some non-motor symptoms related to cognition, pain and sleep. (9). There is some evidence from experimental and clinical study of PD patients that demonstrate the dopaminergic determination for some non-motor features of PD.

One PET study with 11 C – raclopride demonstrate, in vivo, dopaminergic dysfunction in the hypothalamus of PD patients (8). Recently, the RECOVER study has used non-motor symptoms as a primary and secondary end point measures. This study shows up good effect of dopaminergic therapy (dopamine agonists) on sleep. Some reports of EUROPAR research group, including patients using subcutaneous apomorphine and intrajejunal levodopa infusions, show a robust effect on NMSS subdomains like sleep, mood and pain in addition to the expected motor improvement (9,10).

According to the six stages pathological process based on Lewy body formation and deposition from caudal to rostral structures (Braak), the appearance of non-motor features in „pre-motor" phase of PD is explained by involvement of lower brainstem nuclei and connections (11).

In Braak stage 1 there is degeneration in the olfactory bulb, anterior olfactory nucleus and the dorsal nucleus of the vagus in the medulla. Braak stage 2 reflects progression to the lower brainstem and affect areas related to sleep homeostasis, depression, cognition, and pain. Sleep disorders are related to abnormalities of sleep-wake cycle related

pathways mediating thalamocortical arousal. The peduculopontine nucleus, locus coeruleus and serotoninergic raphe nuclei are thought to be key areas related to visual hallucinations and REM sleep behaviour disorder (12).

Prospective strong evidence suggest that olfactory problems, rapid eye movement sleep behaviour disorder (RBD), constipation and depression may predate the motor signs of Parkinson's disease. Other possible „premotor" symptoms are: visual disturbances, apathy, fatigue, excessive daytime sleepiness (13).

In the last two stages of disease (stage 5 and 6), according to the model proposed by Braak and colleagues, the presence of hallucinations and dementia can be explained by the occurence of typical lesions at both cortical and subcortical level (diencephalon, limbic cortex) (14).

The "neurotoxic" hypothesis can be sustained by the results of recent research conducted in animal models of parkinsonism. The study of pesticides, in particular paraquat and rotenone as causative agents for PD, gain significant attention when it was discovered that they are toxicologically or structurally similar to MPTP (1-metil-4 phenyl-1-,2,3,6- tetrahydropiridine) (15).

Recent studies have focused on observations that aggregated alfa -synuclein protein, the major component of Lewy bodies is found throughout the nervous system. It is speculated that misfolded alfa-synuclein transfers between cells in a prion-like manner, thereby mediating the spread of the neuropathology (16).

Neurologists must differentiate between non-motor symptoms and fluctuations of non-motor type that are dopamine dependent and can be improved by levodopa therapy. These non-motor fluctuations have been classified to three subtypes: dysautonomic, cognitive/psychiatric and sensory/pain. The cause appears to be secondary to pulsatile dopaminergic therapy. (17). The most frequent non-motor fluctuations were: anxiety (66%), drenching sweats (64%), slowness of thinking (58%), fatigue and akathisia (54%). Wearing-off questionnaire (WOQ) can be a good clinical tool for diagnosis of non-motor fluctuations.

EVALUATION OF NON-MOTOR SYMPTOMS IN PARKINSON DISEASE

The Parkinson Disease Non-Motor Group (PD-NMG) has developed and validated the first self-administered screening tool to detect the presence of NMS: NMSQuest. This tool consists of 30 items classified in 10 domains but not a grade - rating tool. So, for the comprehensive evaluation of NMS, the same group developed a scale – the PD non-motor symptoms scale (NMSS) that explores nine domain (cardiovascular, sleep/fatigue, mood, cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual and miscellaneous). Items are scored for frequency and severity and the total sum may be obtained for each domain and for the whole scale.

SCOPA programme address also the unmet need of assessment tools for NMS in PD and has developed and validated clinimetrically sound rating scales for PD which address some non-motor domains of the disease such sleep, depression, anxiety, autonomic dysfunction, pain and psychosocial factors. But these scales do not provide a comprehensive assessment of NMS like NMSQuest.

Movement Disorders Society modified the existing UPDRS to include eleven non-motor symptoms (e.g. anxiety, somnolence, disturbances of sleep, urinary and bowel functions).

THE SPECTRUM OF NON-MOTOR SYMPTOMS IN PARKINSON DISEASE

Sleep disturbances

The causes are multifactorial but the main pathological mechanisms is the degeneration of some CNS structures responsible for sleep, in the brainstem (pedunculopontine, locus coeruleus and the retrorubral nucleus) together with thalamocortical pathways.

Nocturnal disturbances may be defined as the following three types:

1. PD related motor symptoms:
   - Nocturnal akinesia, early morning dystonia, painful cramps
   - Optimization of dopatherapy seems to be useful

2. Nocturnal behaviour disturbances (agitation, confusion):
   - Due to presence/treatment of psychiatric symptoms such hallucinations, anxiety and depression
   - Adjustment of therapy and specific treatments can be useful

3. Other sleep disorders:
- Insomnia (37%)
- RBD (30%)
- Excessive daytime sleepiness
- PMLS (periodic movement of limbs during sleep including the Restless Legs Syndrome (RLS), present in 15 % of PD patients (6)

Insomnia has a multifactorial determination: motor symptoms, RLS, nocturia, respiratory disorders (obstructive sleep apnea syndrome).

PMLS and its most common clinical manifestation – RLS, may be associated also to a dopaminergic dysfunction and responds to dopatherapy.

Parasomnias are undesirable behaviours occurring exclusively during sleep or exaggerated by sleep. They include vivid dreams, altered dream content, nightmares, night terrors, nocturnal vocalization, RBD, nocturnal hallucinations; the last two are more prevalent in patients with PD. RBD (REM sleep behaviour disorder) is present in about one third of patients with PD and is characterized by the loss of normal skeletal muscle atonia during REM sleep. Sometimes it may be amplified by dopatherapy. The clinician should pay attention to occurrence of vivid dream because it is the forewarning sign of hallucinations and levodopa-induced psychosis. RBD may precede the development of the motor signs of Parkinson's disease in about 40 % of cases.

Excessive daytime sleepiness. Causal factors are: insomnia, depression, dysautonomia (nocturnal hyperhidrosis and nocturia) and some drugs. This symptom is also associated with cognitive disorder and depression, long duration of levodopa therapy and hallucinations.

Depression

Depending on the criteria used, depression may be present in up to 10-45 % of patients with PD. The probable mechanisms are: damage of serotoninergic pathways as well as limbic noradrenergic and dopaminergic mechanisms (19).

The clinical manifestations of depression in PD are different to the classical features of the depressive disease. In PD patients, the predominant features are somatic (lack of energy, psychomotor slowing), with irritability but usually with no guilty and failing feeling (20). Suiccidal ideas are often present and suiccid is possible, in particular in younger patients, but less frequent as in the depressive psychosis probably due to the co-existence of anxiety which is another feature of PD (see below).

Depression may involve specific neuronal pathways: raphe nuclei (serotoninergic), locus coeruleus (noradrenergic), amygdala, cingular cortex, mesolimbic and mesocortical mesothalamic pathways (dopaminergic) (21).

Anxiety

Anxiety is two times more frequent in PD compared to the general population. The presence of anxiety symptoms has been found in 20 to 46 % of PD patients.

Risk factors for anxiety disorders are female gender, presence of motor fluctuations and previous anxiety disorder. Anxiety may be related to motor fluctuations and can worsen other parkinsonian symptoms such cognitive but also motor symptoms.

Apathy

Apathy consists in a loss of motivation, which appears in emotional, intellectual domains and in the behaviour. Apathy may be assessed by the decrease of voluntary behaviours, that is, behaviours effectively decided by the patient himself, and not induced by other persons (22).

Apathy and depression partially overlap.The relationship between the incidence of apathy and the decrease of dopamine mediation is stronger during the earliest stages of the disease (27). With more advanced stages of the disease the cognitive decline could contribute to the apathetic behaviour, through dysexecutive dysfunction (1).

DOPAMINE DYSREGULATION SYNDROME (DDS) AND IMPULSE CONTROL DISORDERS (ICD)

The definition of **DDS** reffers to the compulsive use of dopaminergic drugs, associated with severe behavioural symptoms and impaired social functioning. **ICD** are behavioural disorders characterized by failure to resist an impulse, inability to cut down and unsuccessful attempts to control a specific behaviour and include pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating and punding (repetitive handling, examining, sorting and arranging of objects – a kind of fascination of doing nothing) (23).

These symptoms are not so frequent (4%) but they affect the quality of life of patients and their family, and have to be taken account before initiat-

ing dopaminergic therapy in a young PD patient (22). These behavioural problems appear more frequent in association with dopamine agonist therapy and individual vulnerability (male gender, younger age, impulsivity). Several hypotheses have been proposed to underlie those abnormal behaviours. Dopaminergic treatment titrated to alleviate motor dorsal striatal deficiencies probably may result in an "over-dosing" in ventral corticostriatal cognitive and limbic pathways.

Cognitive decline

Cognitive disorder imply dysfunction of substantia nigra and nigrostriatal pathway but also the alteration of ascending cholinergic and catecholaminergic neuronal systems and the degenerative pathology of the brain cortex. Frontal subcortical syndrome is characterized by deficit of behavioural regulation of sorting or planning tasks, defective use of memory stores and impaired manipulation of internal representation of visuospatial stimuli (23).

Dementia may be present during the advanced stage of PD and have some significant predictors such older age of onset of the disease and increased severity of motor symptoms.

Cortical activity of choline acetiltransferase is reduced and cholinergic inhibitors have been shown to have a beneficial effect on cognition in PD dementia.

Hallucinations, delusions and psychosis

Hallucinations occur usually in a normal state of consciousness, without delirium and have a chronic course. The most frequent are visual and may be identified by systematically questioning the patient (25). They are not recognized by the patient when alterations of cognitive faculties or dementia are also present. Frequently, they are mostly induced by dopaminergic therapies, in particular by dopamine agonists. It is now admitted that specific factors of the disease may contribute to the appearance of hallucinations.

- Hypersensitization of dopamine receptors in frontal and limbic areas;
- Lesions in the pedunculopontine, locus coeruleus, dopaminergic raphe nuclei, lingual gyrus and superior parietal lobe (24).

Pain

Pain is one of the most frequent NMS at onset of the disease and may precede the onset of motor parkinsonian symptoms. After adjustment concerning ostheoarticular comorbidity, pain is estimated to be twice more frequent in PD patients than in patients without PD (25).

Ha and Jancovic (26) classify the pain syndrome in Parkinson disease as:

- **Musculoskeletal** – that may be associated with rheumatologic and orthopedic disease;
- **Dystonic** – that may fluctuate with medication;
- **Radicular or neuropathic pain;**
- **Central or primary pain** – that may have autonomic features and can be a type of non-motor fluctuation;
- **Akathisia –** may fluctuate with medication effect, and is improved by levodopa (27).
- **Other types of pain (oral, genital)** manifest as sensory wearing off.

Not only levodopa—related dystonia, but also other types of pain (akathisia, musculoskeletal pain related to rigidity and akinesia) respond to optimization of levodopa therapy. Other neurotransmitters may also contribute to pain in PD, such as noradrenalin, serotonin, glutamate transmission and opioid systems (27).

Dysautonomia

Autonomic failure may be an early feature of PD but it is more evident associated with late stages of the disease and include:

Genitourinary dysfunction:

- Lower urinary tract symptoms (urinary frequency, nocturia, urinary incontinence) are in relation with detrusor hyperactivity caused by an altered dopamine basal ganglia circuit;
- Sexual dysfunction is related to hypothalamic dysfunction via dopamine - oxytocin pathways (28).

Orthostatic hypotension

Orthostatic hypotension is present in 20-58% of patients with PD (29). The main mechanism is the presence of peripheral postganglionic sympathetic dysfunction. Antiparkinsonian drugs (levodopa, dopamine agonists and I-MAO-B) can induce orthostatic hypotension independently of the disease. Otherwise, the early onset of symptomatic orthostatic hypotension is considered as an exclusion criteria for idiopathic PD.

Constipation

Constipation is one of the most commonest non-motor symptoms in PD. Constipation has been reported as a prominent complaint prior to the onset of motor symptoms of PD in about 50% of patients in one series (30). Lewy body pathology in the peripheral autonomic nervous system involving the myenteric plexus with subsequent colonic sympathetic denervation contributes to constipation in PD (31).

CONCLUSIONS

The prevalence of NMS is high if the clinician pay attention to them and examine the patient carefully. Today, we have clinical tools (like NMS-Quest) to identify non-motor symptoms unreported by the PD patients. Non-motor manifestations in Parkinson's disease have mechanisms that may provide different treatment strategies tailored to each patient. Non-motor symptoms are determinant for the quality of life of patients. Severity of disease (Hoehn and Yahr stage >3) is associated with reduction in quality of life, increased disability and increased NMS prevalence (32).

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